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Article

Depressive and Anxiety Symptoms Predict Health-Related Quality of Life More Than Cognitive Impairment After Minor Stroke or Transient Ischemic Attack: A Hierarchical Regression Analysis

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Highlights

- Anxiety and depressive symptoms are highly prevalent after TIA or minor stroke and strongly affect health-related quality of life.
- Cognitive impairment is common but does not independently predict quality of life once mood symptoms are considered.
- Mood and cognitive complications follow separate pathways, highlighting the importance of routine psychological assessment

Abstract

Background. Transient ischemic attack (TIA) and minor stroke often result in excellent functional recovery but are frequently followed by substantial psychological morbidity. It remains unclear whether mood disturbances or cognitive impairment are the primary contributors to reduced health-related quality of life (HRQoL) in this population. **Methods.** We conducted a prospective observational case-control study including 90 patients with acute TIA or minor stroke confirmed by diffusion-weighted imaging, and 92 age-matched healthy controls. At 90 days, participants completed the Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, Montreal Cognitive Assessment, and the EQ-5D-5L. Hierarchical multiple regression using standardized z-scores identified independent predictors of HRQoL. Bias-corrected bootstrapped mediation analyses (5,000 iterations) assessed whether cognitive impairment mediated the relationship between mood symptoms and HRQoL. **Results:** Compared with controls, patients exhibited markedly higher rates of depression (82.2% vs. 18.5%), anxiety (81.1% vs. 21.7%), and cognitive impairment (66.7% vs. 13.0%) (all $p < 0.001$). Psychopathological variables explained an additional 36.6% of HRQoL variance, whereas cognitive and neuroimaging variables contributed only 1.7% ($\Delta R^2 = 0.017$; $p = 0.523$). Anxiety showed the strongest predictive value ($\beta = -0.055$; $p = 0.064$), while cognitive impairment had negligible effects ($\beta = -0.001$; $p = 0.947$). Mediation analyses revealed no significant indirect effects, indicating that mood and cognitive complications arise independently rather than sequentially. **Conclusions:** Following TIA or minor stroke, depressive and anxiety symptoms are highly prevalent, persist despite good neurological recovery, and exert a disproportionately negative impact on HRQoL. Anxiety appears particularly influential in determining patient-reported outcomes, underscoring the need for routine mood screening and targeted psychological management in this population.

Keywords: transient ischemic attack; minor stroke; depression; anxiety; quality of life; hierarchical regression; mediation analysis

1. Introduction

Cerebrovascular disease remains one of the leading global causes of morbidity and disability, with an estimated 11.9 million incident cases each year. (1) Although research has traditionally focused on moderate-to-severe stroke, transient ischemic attacks (TIAs) and minor ischemic strokes represent a substantial proportion of cerebrovascular events, accounting for up to 16% of first-ever cases in population-based cohorts. (2) Historically considered to have minimal long-term consequences due to the absence of significant functional disability (modified Rankin Scale ≤ 2), (3,4) these events are now recognized as potential triggers for persistent psychopathological symptoms and cognitive impairment, even in patients with excellent neurological recovery and no recurrent vascular events.(5,6)

Post-stroke depression is among the most prevalent neuropsychiatric complications in this population, affecting 11% to 42% of individuals after TIA or minor stroke depending on study design, timing, and patient characteristics. (7–10) Anxiety is also common, reported in 12% to 30% of cases, and frequently co-occurs with depressive symptoms in a bidirectional pattern that amplifies emotional distress and functional difficulties. (9,11,12) Importantly, these symptoms can arise even in the absence of detectable physical disability, implicating mechanisms beyond motor impairment, including neurobiological alterations, inflammatory pathways, and psychosocial stressors. (13,14)

Cognitive impairment is another frequently under-recognized sequela, reported in approximately 30–54% of TIA and minor stroke survivors (15–18) often coexisting with depressive and anxiety symptoms. Although cross-sectional studies (15,16) have been conducted, no previous study has directly evaluated whether cognitive impairment causally precedes mood alterations, contributes independently to emotional difficulties, or whether these complications emerge as parallel consequences of cerebrovascular injury.

Mood disturbances have a substantial impact on health-related quality of life (HRQoL), functional independence, return to work, and rehabilitation engagement. (17) In patients with severe stroke, the HRQoL is primarily influenced by motor and functional limitations. However, the mechanisms underlying HRQoL reductions in minor cerebrovascular events, where physical disability is minimal, remain poorly characterized.

Despite evidence linking depression, anxiety, and cognitive impairment to HRQoL after minor stroke, the relative contributions of these factors and potential pathways connecting them remain unclear. Mediation analysis offers a suitable approach to clarify whether (1) cognitive impairment leads to mood disturbances that subsequently reduce HRQoL, (2) cognitive impairment and mood disturbances exert independent effects, or (3) both mechanisms operate concurrently.

The present study aimed to quantify the burden of psychopathological and cognitive complications following minor cerebrovascular events, identify the determinants of HRQoL, and examine whether mood symptoms mediate the relationship between cognitive impairment and HRQoL. Additionally, we assessed the utility of neuroimaging biomarkers as predictors of neuropsychiatric and cognitive outcomes in this population.

2. Materials and Methods

Study Design and Participants

We conducted a single-center, prospective, observational case–control study. Consecutive patients aged 18–70 years presenting with acute TIA or minor ischemic stroke (NIHSS ≤ 4) and confirmed by magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) were enrolled.

Exclusion criteria included prior dementia, significant pre-existing disability (pre-morbid modified Rankin Scale [mRS] >1), and inability to communicate in Spanish. Controls were age-matched individuals with no history of cerebrovascular events, dementia, or major neurological disease.

This study adhered to the STROBE reporting guidelines, and the protocol was approved by the Ethics Committee of the University Hospital of Badajoz (Spain). Written informed consent was obtained from all participants.

Demographic characteristics, vascular risk factors, and neurological status—including NIHSS subscores for consciousness, language, and motor function, —were collected. The functional status at discharge was assessed using the mRS. Standardized physical measurements (blood pressure, height, weight, and body mass index) were obtained according to institutional protocols. Laboratory studies performed on admission included plasma glucose, urea, creatinine, estimated glomerular filtration rate, total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride levels.

All clinical and psychopathological assessments were performed by trained evaluators who underwent standardized study-specific training to ensure inter-rater consistency.

Neuroimaging Acquisition and Analysis

All patients underwent brain MRI in the acute phase (mean 1.3 ± 0.8 days post-event) using a Philips Intera 1.5-Tesla scanner. The protocol included:

DWI: presence, number, and location of acute ischemic lesions

Apparent diffusion coefficient (ADC) maps: confirmation of acute ischemia

FLAIR: quantification of white matter hyperintensities using the Age-Related White Matter Changes (ARWMC) scale

T2-weighted gradient echo: presence, number, and location of cerebral microbleeds

Neuroimaging analyses were performed by experienced neuroradiologists who were blinded to all clinical and psychopathological outcomes. Image quality was reviewed systematically, and cases with incomplete or non-diagnostic sequences were excluded from imaging-based analyses.

Psychopathological, Cognitive, and HRQoL Assessment

All assessments were conducted 90 ± 14 days after the index event by evaluators blinded to neuroimaging findings.

Depression: Hamilton Depression Rating Scale (HDRS-17); scores > 7 defined depressive symptoms.

Anxiety: Hamilton Anxiety Rating Scale (HAM-A); clinically relevant anxiety defined as HAM-A ≥ 7 , consistent with prior work in post-stroke populations.

Cognition: Montreal Cognitive Assessment (MoCA; 30-point scale); scores < 26 defined cognitive impairment. The MoCA has been validated in Spanish-speaking patients with TIA/minor stroke.

Health-related quality of life (HRQoL): EuroQol EQ-5D-5L utility index and visual analogue scale (EQ-VAS, 0–100). EQ-5D-5L utility values were derived using the Spanish value set.

To minimize interviewer-related bias, all psychopathological scales were administered following a standardized structured protocol.

Statistical Analysis

Continuous variables are expressed as mean $\pm$ SD or median [IQR], and categorical variables as numbers (%). Between-group comparisons used independent-samples *t* tests or Mann–Whitney U tests, and χ^2 or Fisher's exact tests were used for categorical variables. Effect sizes were expressed as Cohen's *d* and odds ratios (ORs) with 95% confidence interval (CIs). Statistical significance was set at $p < 0.05$.

Among the cases, bivariate associations were examined using Pearson or Spearman correlation coefficients, depending on the variable distribution and scale. Correlation strength was interpreted as weak ($|r| < 0.30$), moderate (0.30 – 0.70), or strong (> 0.70). False-discovery-rate-adjusted *q* values are provided in Supplementary Tables.

Regression Modeling

Independent predictors of HRQoL (EQ-5D-5L utility index) were examined using hierarchical multiple linear regression. Three nested models were prespecified as follows:

Sociodemographic/clinical: age, sex, mRS, social risk

Psychopathological: HDRS-17, HAM-A

Cognitive/neuroimaging: MoCA, presence of DWI lesions, prior silent infarcts

Continuous predictors were standardized (z-scores); binary variables were coded 0/1. Model fit was evaluated with R^2 , adjusted R^2 , ΔR^2 , and incremental F tests. For each predictor, we report the standardized (β) and unstandardized (B) coefficients, SE, 95% CI, t , and p values.

Model assumptions (linearity, homoscedasticity, normality of residuals, independence, and multicollinearity) were systematically checked. No violations that affected the inference were detected. Sensitivity analyses included HC3-robust standard errors and beta-regression to account for the bounded EQ-5D-5L distribution; findings were unchanged.

Mediation Analysis

Psychological mediation pathways were evaluated using non-parametric bootstrapped mediation. Two models were tested: a) MoCA $\rightarrow$ HDRS-17 $\rightarrow$ EQ-5D-5L and b) MoCA $\rightarrow$ HAM-A $\rightarrow$ EQ-5D-5L.

All variables were standardized, and age and sex were included as covariates. Indirect effects were considered significant if the 95% bootstrap confidence interval (CI) excluded zero.

Mediation analyses were conducted using PROCESS v3.5 (SPSS v29) with 5,000 bias-corrected accelerated bootstrap resamples; all other analyses were performed in R (v4.3.0).

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

3. Results

Sample Characteristics

A total of 182 participants were enrolled, including 90 patients with acute TIA or minor ischemic stroke (NIHSS ≤ 4) and 92 age matched healthy controls. The case group had a significantly higher proportion of males (73.3% vs. 45.7%; $\chi^2 = 13.32$; $p < 0.001$) and a greater prevalence of hypertension (58.9% vs. 37.0%; $p = 0.003$), diabetes mellitus (28.9% vs. 15.2%; $p = 0.037$), current smoking (63.3% vs. 38.0%; $p < 0.001$), and prior ischemic heart disease (13.3% vs. 1.1%; $p = 0.004$). Among cases, acute DWI lesions were present in 72.2% ($n = 65$), previous silent infarcts in 28.9% ($n = 26$), and cerebral microbleeds in 7.8% ($n = 7$). The baseline characteristics are summarized in Table 1, with extended imaging descriptors in Table S1 (baseline block).

Table 1. Baseline demographic characteristics, cardiovascular risk factors, and family history of cases and controls.

Variable	Cases (n = 90)	Controls (n = 92)	<i>p</i> value
Demographic characteristics			
Male sex, n (%)	66 (73.3)	42 (45.7)	<0.001
Age, years, mean $\pm$ SD	59.3 $\pm$ 8.2	58.6 $\pm$ 7.8	0.562
Urban residence, n (%)	43 (47.8)	57 (62.0)	0.055
Educational level, n (%)			0.005
– Literate without formal education	37 (41.1)	20 (21.7)	
– Primary or secondary education	50 (55.6)	61 (66.3)	
– University education	3 (3.3)	11 (12.0)	
Social situation, n (%)			0.037
– Good or acceptable	59 (65.6)	73 (79.3)	
– Social risk	31 (34.4)	19 (20.7)	
Cardiovascular risk factors			
Hypertension, n (%)	52 (57.8)	33 (35.9)	0.003
Dyslipidemia, n (%)	38 (42.2)	29 (31.5)	0.135
Diabetes mellitus, n (%)	26 (28.9)	15 (16.3)	0.042
Atrial fibrillation, n (%)	10 (11.1)	8 (8.7)	0.585
Prior ischemic heart disease, n (%)	11 (12.2)	1 (1.1)	0.002
Current tobacco use, n (%)	57 (64.0)	35 (38.0)	<0.001

Alcohol consumption, n (%)	50 (56.2)	39 (42.4)	0.064
Family history			
History of stroke, n (%)	25 (27.8)	27 (29.3)	0.815
History of ischemic heart disease, n (%)	29 (32.2)	30 (32.6)	0.956

Values are presented as *mean ± standard deviation* or *number (percentage)*. *p* values were calculated using Student’s *t* test for continuous variables and the χ^2 test or Fisher’s exact test for categorical variables, as appropriate. Statistical significance was set at *p* < 0.001.

Psychopathological, Cognitive, and HRQoL Outcomes at 90 Days

Depressive (HDRS 17 ≥ 7) and anxiety symptoms (HAM A ≥ 7) were significantly more prevalent in cases than controls (depression: 82.2% vs. 18.5%; χ^2 = 71.42; *p* < 0.001; anxiety: 81.1% vs. 21.7%; χ^2 = 61.82; *p* < 0.001). Patients also showed higher mean symptom scores (HDRS 17: 11.86 ± 5.84 vs. 4.13 ± 4.35, *p* < 0.001, *d* = 1.50; HAM A: 13.60 ± 7.57 vs. 4.64 ± 5.58, *p* < 0.001, *d* = 1.35). Cognitive impairment (MoCA < 26) was more frequent among cases (66.7% vs. 13.0%; χ^2 = 52.49; *p* < 0.001), with lower mean MoCA scores (24.08 ± 3.26 vs. 27.21 ± 2.36; *p* < 0.001, *d* = -1.10). HRQoL (EQ 5D 5L utility) was markedly reduced in cases (0.847 ± 0.152) compared with controls (0.974 ± 0.076; *p* < 0.001, *d* = -1.05). These contrasts are summarized in Figure 1 and, in greater detail (including Cohen’s *d*, ORs, and 95% CIs), in Table S1. The case–control prevalences are shown in Figure S1, Panel A.

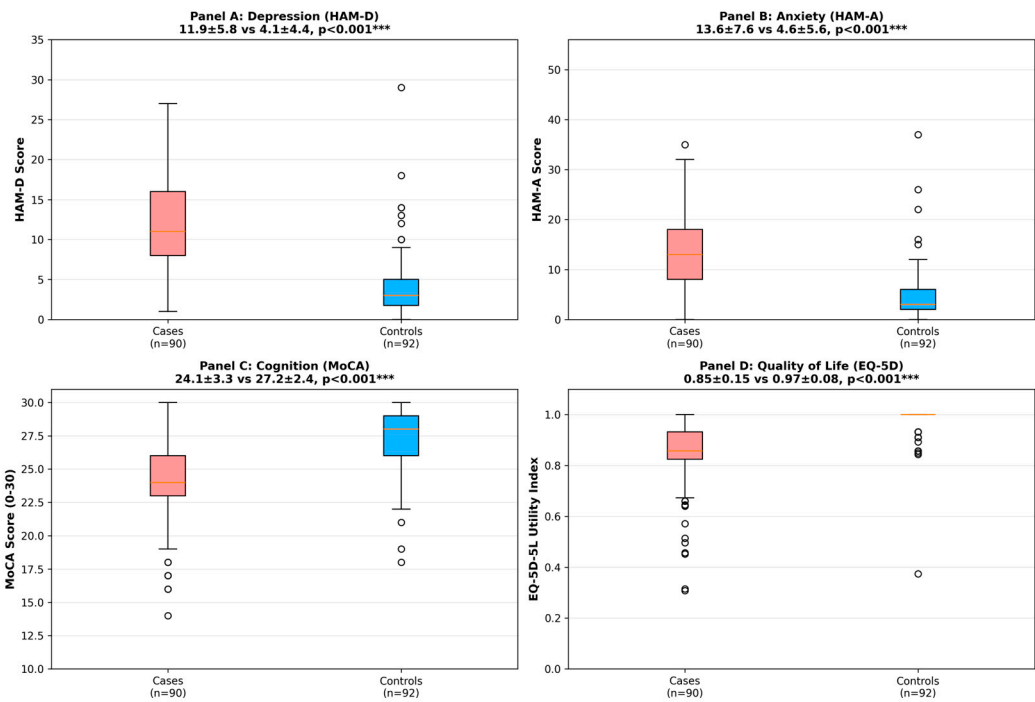


Figure 1. Comparison of Depressive Symptoms, Anxiety, Cognition, and Quality of Life Between ATI/Minor Stroke Patients and Healthy Controls. Comparison of depressive symptoms (HDRS-17), anxiety (HAM-A), cognitive performance (MoCA), and quality of life (EQ-5D-5L) between ATI/minor stroke patients (*n* = 90) and healthy controls (*n* = 92). Boxes represent median and interquartile range; whiskers indicate minimum and maximum values, excluding outliers. Group comparisons were performed using independent-samples tests as appropriate. *p* < 0.001.

Bivariate Associations

Within cases, mood scores showed strong negative associations with HRQoL (HDRS 17 vs. EQ 5D 5L *r* = -0.612, *p* < 0.001; HAM A vs. EQ 5D 5L *r* = -0.625, *p* < 0.001), and HDRS 17 correlated strongly with HAM A (*r* = 0.681, *p* < 0.001), whereas correlations between MoCA and HRQoL were

negligible ($r = 0.092$, $p = 0.372$). The complete correlation matrix (including correlation type and FDR adjusted q values) is provided in Table S2 and is graphically displayed in Figure S1, Panel B.

Predictors of HRQoL: Hierarchical Regression

Among cases with complete data ($n = 89$), Model 1 (age, sex, mRS and social risk) accounted for 6.1% of the HRQoL variance ($F = 1.36$; $p = 0.256$). Adding depressive and anxiety symptoms to Model 2 significantly increased the explained variance ($\Delta R^2 = 0.366$; total $R^2 = 0.427$; $F = 10.18$; $p < 0.001$). Model 3, which added MoCA, DWI lesion status, and prior silent infarcts, contributed minimally ($\Delta R^2 = 0.017$; $R^2 = 0.444$; $F = 7.02$; $p < 0.001$); the increment over Model 2 was not significant ($\Delta R^2 = 0.017$; $p = 0.523$). Model level metrics are presented in Table 2 and Table S4; full coefficients for Model 3 (β , B , SE , 95% CI , t , p) in Table 3 and Table S5. Diagnostics (VIFs, residual analyses, and heteroscedasticity tests) and sensitivity analyses (HC3 robust estimates and beta regression models) are provided in Tables S6–S7. Figure 2 illustrates the stepwise increase in R^2 (Panel A) and the standardized coefficients for the final model (Panel B).

Table 2. Hierarchical Regression Model Comparison: Incremental Variance Explained in Quality of Life Prediction.

Model	Predictors included	R ²	Adjusted R ²	F statistic	p value	ΔR ²
Model 1	Age, sex, mRS, social risk	0.061	0.016	1.36	0.256	—
Model 2	Model 1 + HDRS-17, HAM-A	0.427	0.385	10.18	<0.001	0.366
Model 3	Model 2 + MoCA, DWI lesion burden, number of infarcts	0.444	0.381	7.02	<0.001	0.017

R^2 indicates the proportion of variance that is explained by the model. ΔR^2 represents the incremental change in the explained variance relative to the previous model. mRS: modified Rankin Scale; HDRS-17: Hamilton Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; MoCA: Montreal Cognitive Assessment; DWI: diffusion-weighted imaging.

Table 3. Standardized Regression Coefficients for Predictors of Quality of Life.

Predictor	Standardized β	SE	95% CI	p value
Anxiety (HAM-A)	−0.055	0.029	−0.114 to 0.003	0.064†
Social risk	−0.048	0.029	−0.105 to 0.009	0.100
Depression (HDRS-17)	−0.043	0.029	−0.102 to 0.016	0.147
DWI lesion burden	0.050	0.033	−0.016 to 0.116	0.133
Silent infarcts	0.015	0.030	−0.046 to 0.075	0.627
Age	0.006	0.014	−0.022 to 0.033	0.686
Sex	−0.000	0.031	−0.062 to 0.061	0.990
mRS	−0.001	0.021	−0.044 to 0.041	0.947
MoCA	−0.001	0.014	−0.029 to 0.027	0.947

The values represent the standardized regression coefficients (β). 95% CI indicates the 95% confidence interval. †Trend toward statistical significance ($p < 0.10$). HAM-A: Hamilton Anxiety Rating Scale; HDRS-17: Hamilton Depression Rating Scale; mRS: modified Rankin Scale; MoCA: Montreal Cognitive Assessment; DWI: diffusion-weighted imaging.

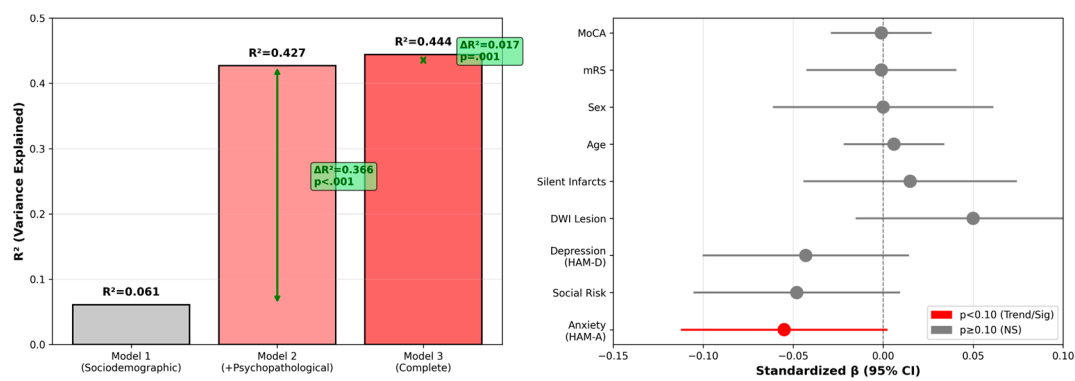


Figure 2. Hierarchical Regression Analysis: Model Progression and Predictor Contribution. Hierarchical regression model performance and standardized coefficients. Panel A shows the variance explained (R^2) for each incremental model and the corresponding change in explained variance (ΔR^2). Panel B displays the standardized regression coefficients (β) and 95% confidence intervals for the predictors in the final model. Red markers denote trend-level effects ($0.05 \leq p < 0.10$). HAM-A: Hamilton Anxiety Rating Scale; HDRS-17: Hamilton Depression Rating Scale; mRS: modified Rankin Scale; MoCA: Montreal Cognitive Assessment; DWI: diffusion-weighted imaging.

Mediation Analysis

In the depression model (Model A), MoCA was not associated with HRQoL ($\beta = 0.056$; $p = 0.609$) or depression severity (a path $\beta = -0.095$; $p = 0.331$). Depression was associated with lower HRQoL (b path $\beta = -0.060$; $p = 0.034$). The indirect effect was small and non significant ($\beta = -0.006$; 95% BCa CI -0.068 to 0.047). Similarly, in the anxiety model (Model B), MoCA was not associated with anxiety (a path $\beta = -0.127$; $p = 0.239$), whereas anxiety predicted lower HRQoL (b path $\beta = -0.062$; $p = 0.041$). The indirect effect was non significant ($\beta = 0.008$; 95% BCa CI -0.046 to 0.078).

Path level estimates (c, a, b, c') and bootstrap intervals are detailed in Tables S3A–S3B; and the standardized path diagrams are show in Figure 3.

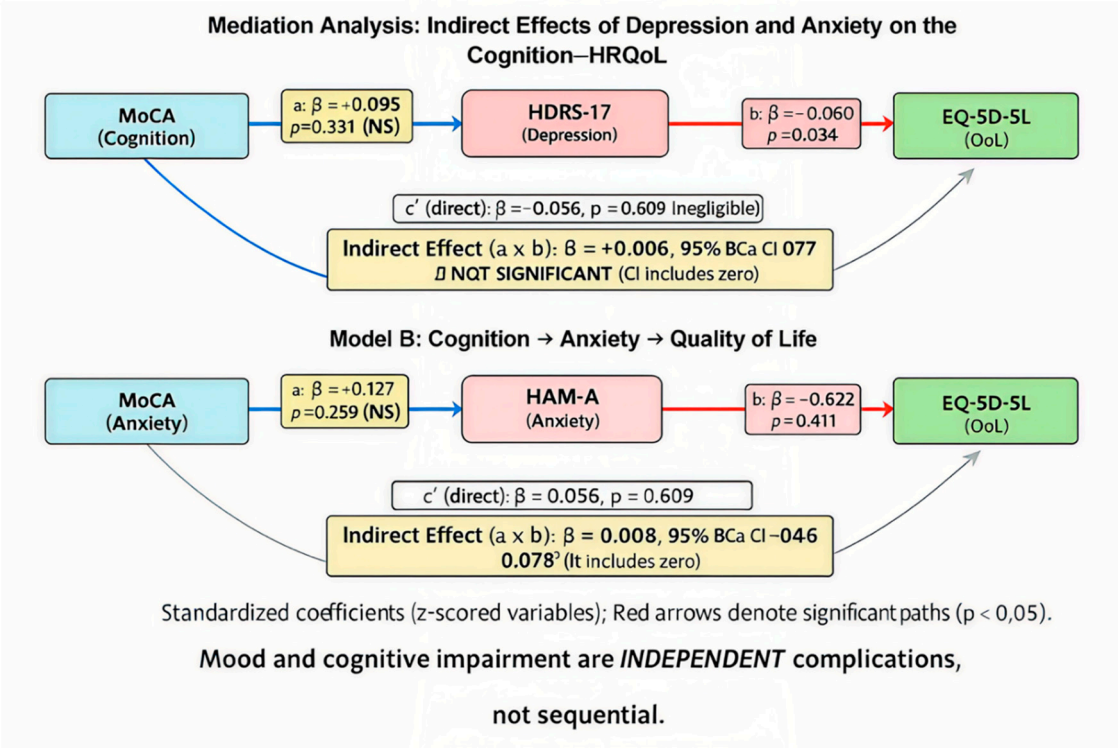


Figure 3. Mediation Analysis: Indirect Effects of Depression and Anxiety on the Cognition–Health-Related Quality of Life Relationship. Legend: Model A (MoCA → HDRS-17 → EQ-5D-5L): a-path $\beta = -0.095$, $p = 0.381$; b-path $\beta = -0.060$, $p = 0.034$; indirect effect $\beta \approx +0.006$ (95% BCa CI -0.068 to 0.047), not significant; direct effect c' (MoCA → HRQoL) $\beta = 0.056$, $p = 0.609$. Model B (MoCA → HAM-A → EQ-5D-5L): a-path $\beta = -0.127$, $p = 0.239$; b-path $\beta = -0.062$, $p = 0.041$; indirect effect $\beta = 0.008$ (95% BCa CI -0.046 to 0.078), not significant; direct effect c' $\beta = 0.056$, $p = 0.609$. All coefficients are standardized (z-scored variables). Red arrows denote significant paths ($p < 0.05$); blue/gray arrows denote non-significant paths. These models show no significant indirect effects, indicating that mood symptoms and cognitive impairment are parallel, independent complications after TIA/minor stroke.

Sex stratified analysis.

Sex specific means for HDRS 17, HAM A, MoCA, and EQ 5D 5L are presented in Figure S1, Panel C; statistical tests and effect sizes are reported in Table S1 (sex stratified block). This analysis complements the primary models and allows assessment of potential sex related differences in clinical profiles.

4. Discussion

This study highlights a notable paradox in the outcomes following TIA and minor ischemic stroke. Despite excellent functional recovery, with nearly 60% of patients achieving a mRS score of 0 (4), a substantial and clinically significant burden of psychopathological and cognitive complications remains. ((26) We observed a high prevalence of depression (82.2%) and anxiety (81.1%) symptoms, as well as cognitive impairment (66.7%), far exceeding rates in age-matched healthy controls (18.5%, 21.7%, and 13.0%, respectively), with effect sizes ranging from 1.10 to 1.50, indicating clinical significance far beyond statistical importance. These findings challenge the traditional labeling of TIA and minor stroke as “benign” and provide important context for interpreting post-event outcomes.

The high prevalence of depressive (82.2%) and anxiety (81.1%) symptoms observed in our cohort aligns with studies that used symptom-based thresholds rather than diagnostic criteria, which typically yield higher estimates than interview-based diagnoses. Recent syntheses show that scale-based screening tends to identify a larger symptomatic burden than clinical interviews, underscoring that threshold selection materially influences prevalence estimates and clinical interpretation.(33) Moreover, contemporary evidence indicates that stroke survivors have nearly threefold higher odds of depression than the general population, reinforcing that elevated symptom rates are epidemiologically plausible rather than artifacts of measurement.(34)

Our findings are also consistent with recent work highlighting lasting impairments after TIA or minor stroke—including depression, anxiety, fatigue, and cognitive change—which remain underrecognized and inconsistently treated. This evolving literature provides a broader context for our results, suggesting that substantial psychological morbidity persists despite minimal neurological deficits. (35)

The prevalence of depressive symptoms in our cohort exceeds that reported in studies using comparable symptom-based assessments (~60%) (27) and is substantially higher than estimates from studies focusing on clinically diagnosed depression (11–41%), likely reflecting methodological differences in outcome definition.(7,28,29) Notably, a high burden of depressive symptoms was observed independent of objective stroke severity (NIHSS ≤ 4), indicating that low stroke severity does not preclude psychological morbidity. Although the mean HDRS score (11.86 ± 5.84 in cases vs. 4.13 ± 4.35 in controls) fell within the mild depressive symptom range, the large effect size observed (Cohen’s $d=1.50$) supports the clinical relevance of these symptoms. Importantly, the use of higher diagnostic cut-offs in previous studies may have led to under-identification of patients with milder depressive symptoms, which can still impact function and HRQoL, without meeting criteria for clinically diagnosed depression.

Similarly, the 81.1% prevalence of anxiety symptoms represents a substantial burden that has been infrequently quantified in minor stroke or TIA populations, where the reported prevalence

ranges from 20-55%. (9,12,30) Anxiety has historically been under-investigated compared to depression or cognitive outcomes. These findings are consistent with neurobiological evidence that even minor ischemic events may trigger inflammatory cascades and neuroplastic changes that increase vulnerability to mood dysregulation. (13) The large independent effect sizes for both depression and anxiety indicate that post-stroke mood symptoms could represent relevant neuropsychiatric outcomes rather than merely secondary consequences of stroke. (35)

Cognitive impairment (MoCA <26) was detected in 66.7% of cases, a prevalence substantially exceeding that observed in control populations and at the upper end of the range reported in minor stroke or TIA populations (30-67%). (6,24,26) The lack of association between cognitive impairment and depression or anxiety in the mediation analysis (indirect effect $p > 0.05$) suggests that cognitive dysfunction represents an independent neurobiological consequence of cerebrovascular injury rather than a secondary manifestation of mood disturbance. This distinction raises the possibility that cognitive dysfunction and mood symptoms may arise through partially independent causal pathways, with implications for targeted cognitive and psychological interventions in patients with TIA.

The absence of mediation by cognition in our models is compatible with recent longitudinal data showing that a single adjudicated, DWI-negative TIA is associated with subsequent cognitive decline independent of vascular and demographic factors, implying that cognitive and affective trajectories may be at least partially dissociable.(36) This supports our interpretation that mood and cognitive complications can arise through parallel pathways, each warranting specific monitoring and intervention.(35)

Although DWI lesions were present in 72.2% of cases and prior silent infarcts in 28.9%, these neuroimaging findings contributed minimally to HRQoL outcomes, suggesting that structural abnormalities do not necessarily predict symptom burden or functional impact and may be driven by neurobiological mechanisms.

A key finding of this study is the predominant contribution of psychopathological symptoms, particularly anxiety and depression, to HRQoL, accounting for 36.6% of the incremental variance, compared with the 1.5% explained by cognitive and neuroimaging variables. Once psychopathological variables were accounted for, cognitive impairment and neuroimaging markers provided minimal additional predictive value for HRQoL outcomes ($\Delta R^2 = 0.015$, $p = 0.523$), suggesting that their association with reduced HRQoL is largely mediated or confounded by mood symptoms. These findings indicate that in this patient population, psychological factors are more strongly associated with patient-reported health status and functional well-being than traditional neurological or imaging-based measures.

Additionally, anxiety emerged as the strongest independent predictor of reduced HRQoL ($\beta = -0.0595$, $p = 0.044$), surpassing the effect of depression and identifying a potentially modifiable contributor to patient-reported HRQoL outcomes, being consistent with previous studies in stroke populations.(31) Mediation analyses further indicated that anxiety and depression influence HRQoL through independent, parallel pathways rather than sequential mechanisms, extending previous work on post-stroke psychopathology.

Multiple interacting neuropsychobiological mechanisms after stroke have been implicated in post-stroke anxiety, as well as depression. These include dysregulation of the hypothalamic-pituitary-adrenal axis, impaired neuroplasticity due to endothelial dysfunction and reduced cerebral blood flow, and heightened inflammatory responses characterized by elevated proinflammatory cytokines. In addition, ischemic lesions may cause functional disconnection of prefrontal-limbic networks involved in mood regulation, contributing to heterogeneous anxiety presentations after stroke.(13,14,32) Together, these findings suggest limitations in models that conceptualize post-stroke psychological and cognitive sequelae as consequences of cognitive injury and support a framework in which anxiety, depression, and cognitive impairment are viewed as parallel complications.

A key unmeasured factor in our analysis is fatigue, which has emerged as a frequent and impactful sequela after TIA/minor stroke and is repeatedly identified as a determinant of HRQoL.

Future studies should incorporate validated fatigue measures to clarify potential confounding or mediating roles between mood symptoms and HRQoL and to refine prognostic models beyond psychopathology and cognition. (35)

Clinically, these data reinforce the need for routine mood screening early after TIA/minor stroke and during follow-up, using brief validated tools and establishing referral pathways to evidence-based interventions (e.g., psychological therapies, pharmacotherapy) shown to improve depressive outcomes in post-stroke populations.(33,37) Given the outsized contribution of anxiety and depression to HRQoL, integrating structured screening and treatment into stroke pathways may yield disproportionate gains in patient-reported outcomes relative to strategies focused solely on neurological impairment.(33,37)

Several important limitations that warrant consideration when interpreting findings. First, our case-control design precludes definitive causal inference regarding the temporal relationship between mood and HRQoL. Prospective longitudinal studies tracking mood trajectories would elucidate temporal sequences and allow for stronger causal claims. Additionally, assessment occurred at a single timepoint (90 days post-event), the longitudinal evolution of mood and HRQoL over longer recovery periods remains unknown. Second, the measurement and population considerations may limit generalizability of the findings. Psychological measures relied on self-report instruments that were potentially subject to recall and social desirability bias. Medication use (antidepressants, anxiolytics and other psychotropic medications) was not tracked, representing an important unmeasured confounder. Our sample was recruited from a university hospital and was predominantly male (72.8%), potentially limiting its applicability to community populations or healthcare systems with different demographic compositions. Third, statistical and analytical considerations merit further attention. The hierarchical regression model included nine predictors and 89 participants, maintaining the recommended 10:1 participant-to-predictor ratio and achieving adequate post-hoc statistical power ($1-\beta=0.84$); nevertheless, larger multicenter samples would improve generalizability and allow subgroup analyses. Finally, while mediation analyses indicated independent contributions of mood and cognition to HRQoL, the absence of statistically significant mediation does not definitively prove independence; unmeasured cognitive domains or alternative pathways may also contribute.

5. Conclusions

This study shows that TIA and minor ischemic stroke ($\text{NIHSS} \leq 4$) are associated with a substantial burden of depression and anxiety symptoms, as well as cognitive impairment, which persists despite excellent neurological recovery and is strongly linked to reduced HRQoL. Mood symptoms, particularly anxiety, were more strongly associated with patient-reported outcomes than cognitive impairment or neuroimaging findings. The relative independence of mood and cognitive complications suggests distinct underlying mechanisms and challenges paradigms that focus primarily on neurological recovery when interpreting post-event outcomes. These findings further indicate that HRQoL may be more closely linked to psychological symptoms than to cognitive recovery alone, underscoring the importance of considering mood when evaluating post-event outcomes, which should be the subject of future studies research.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/doi/s1>, Figure S1. Prevalence, correlations, and sex-stratified outcomes at 90 days after TIA/minor stroke, Table S1. Comparison of psychopathological, cognitive, and quality-of-life outcomes (cases vs. controls), Table S2: Correlation matrix among cases (n=90) Table S3A-B. Mediation Analysis and STROBE Checklist — Case-Control Study.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

- TIA: transient ischemic attack
- mRS: modified Rankin Scale
- HRQoL: health-related quality of life
- DWI: diffusion-weighted imaging
- NIHSS: National Institutes of Health Stroke Scale
- HDRS-17: Hamilton Depression Rating Scale
- HAM-A: Hamilton Anxiety Rating Scale
- MoCA: Montreal Cognitive Assessment

Appendix A

Table S1. Comparison of psychopathological, cognitive, and quality-of-life outcomes (cases vs. controls).

Outcome measure	Cases (n=90)	Controls (n=92)	p value	Cohen’s d	OR (95% CI)†
DEPRESSION					
HDRS-17, mean ± SD	11.9 ± 5.8	4.1 ± 4.4	<0.001***	1.50	—
Depressive symptoms (HDRS-17 ≥ 7), n (%)	74 (82.2)	17 (18.5)	<0.001***	—	20.41 (9.60–43.42)
ANXIETY					
HAM-A, mean ± SD	13.6 ± 7.6	4.6 ± 5.6	<0.001***	1.35	—
Anxiety symptoms (HAM-A ≥ 7), n (%)	73 (81.1)	20 (21.7)	<0.001***	—	15.46 (7.50–31.87)
COGNITIVE FUNCTION					
MoCA, mean ± SD	24.1 ± 3.3	27.2 ± 2.4	<0.001***	–1.10	—
Cognitive impairment (MoCA < 26), n (%)	60 (66.7)	12 (13.0)	<0.001***	—	13.33 (6.31–28.21)
QUALITY OF LIFE					
EQ-5D-5L utility index, mean ± SD	0.85 ± 0.15	0.97 ± 0.08	<0.001***	–1.06	—
EQ-VAS, mean ± SD	51 ± 17	79 ± 13	<0.001***	–1.94	—

Abbreviations: HDRS-17=Hamilton Depression Rating Scale (17-item); HAM-A=Hamilton Anxiety Rating Scale; MoCA=Montreal Cognitive Assessment; EQ-VAS=EuroQol Visual Analogue Scale.

***p<0.001 (two-sided). Utilities derived using the Spanish EQ-5D-5L value set.

Table S2. Correlation matrix among cases (n=90).

Variable pair	r (type)	p value	q (FDR)	Strength
MoCA ↔ HDRS-17	−0.146 (Pearson)	0.162	0.216	Weak/NS
MoCA ↔ HAM-A	−0.170 (Pearson)	0.112	0.186	Weak/NS
HDRS-17 ↔ HAM-A	0.681 (Pearson)	<0.001***	<0.001	Strong
HDRS-17 ↔ EQ-5D-5L	−0.612 (Spearman)	<0.001***	<0.001	Strong
HAM-A ↔ EQ-5D-5L	−0.625 (Spearman)	<0.001***	<0.001	Strong
MoCA ↔ EQ-5D-5L	0.092 (Spearman)	0.372	0.372	Negligible
Age ↔ HDRS-17	−0.103 (Pearson)	0.314	0.357	Weak/NS
Age ↔ MoCA	−0.081 (Pearson)	0.445	0.445	Weak/NS
DWI lesion (0/1) ↔ HDRS-17	0.137 (Point-biserial)	0.190	0.216	Weak/NS
DWI lesion (0/1) ↔ MoCA	−0.191 (Point-biserial)	0.078	0.117	Weak/trend

Correlation method chosen by variable scale/distribution (Pearson for approximately continuous/normal, Spearman for ordinal/non-normal, point-biserial for binary–continuous). False discovery rate (FDR) controlled within this table using Benjamini–Hochberg. HDRS-17=Hamilton Depression Rating Scale (17-item); HAM-A=Hamilton Anxiety Rating Scale; MoCA=Montreal Cognitive Assessment; EQ-5D-5L=EuroQol five-dimension five-level index; DWI=diffusion-weighted imaging; NS=non-significant.

Table S3. A. Mediation Analysis: Cognitive Function → Depression → Quality of Life (HRQoL).

Pathway	Coefficient (β)	SE	95% CI	p value
c (Total effect)	0.0560	0.108	[−0.123, 0.235]	0.609
a (Cognition → Depression)	−0.0951	0.108	[−0.310, 0.120]	0.381
c' (Direct effect)	0.0572	0.109	[−0.130, 0.245]	0.602
b (Depression → HRQoL)	−0.0604	0.028	[−0.116, −0.005]	0.034*
a×b (Indirect effect)	−0.0057	—	[−0.068, 0.047]	—

Notes: Standardized (z-scored) variables; covariates: age and sex. Indirect effect estimated via bias-corrected accelerated (BCa) bootstrap with 5,000 resamples. Analyses run with PROCESS v3.5 (SPSS v29). Two-sided tests; $p<0.05$ marked with *. NS = non-significant.

Table S3. B. Mediation Analysis: Cognitive Function → Anxiety → Quality of Life (HRQoL).

Pathway	Coefficient (β)	SE	95% CI	p value
c (Total effect)	0.0560	0.108	[−0.123, 0.235]	0.609
a (Cognition → Anxiety)	−0.1272	0.107	[−0.343, 0.088]	0.239
c' (Direct effect)	0.0787	0.110	[−0.145, 0.303]	0.476
b (Anxiety → HRQoL)	−0.0620	0.030	[−0.121, −0.003]	0.041*
a×b (Indirect effect)	0.0079	—	[−0.046, 0.078]	—

Notes: Standardized (z-scored) variables; covariates: age and sex. Indirect effect estimated via bias-corrected accelerated (BCa) bootstrap with 5,000 resamples. Analyses run with PROCESS v3.5 (SPSS v29). Two-sided tests; $p<0.05$ marked with *. NS = non-significant.

Appendix B

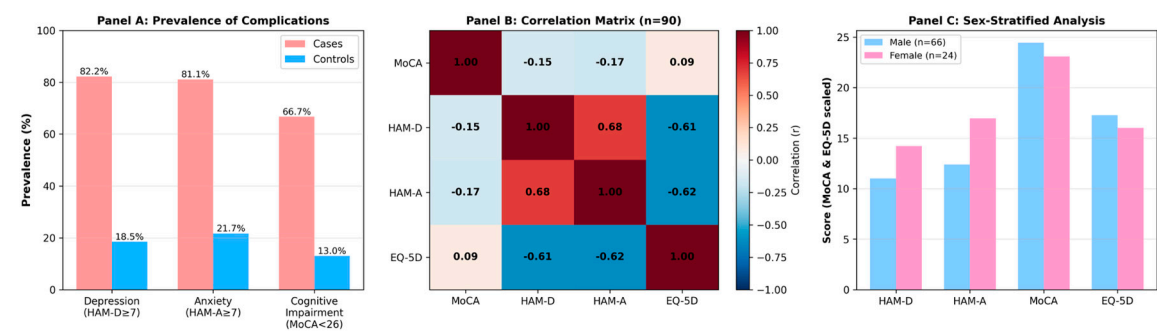


Figure S1. Prevalence, correlations, and sex-stratified outcomes at 90 days after TIA/minor stroke. Three-panel summary. Panel A (Prevalence): Cases vs. controls—depressive symptoms (HDRS-17 ≥ 7), 82.2% vs. 18.5%; anxiety symptoms (HAM-A ≥ 7), 81.1% vs. 21.7%; cognitive impairment (MoCA < 26), 66.7% vs. 13.0%. Panel B (Correlation heatmap, cases n=90): strong associations between mood and HRQoL (HDRS-17 vs. EQ-5D-5L $r = -0.612^{***}$; HAM-A vs. EQ-5D-5L $r = -0.625^{***}$), strong HDRS-17–HAM-A correlation ($r = 0.681^{***}$), and negligible MoCA–EQ-5D-5L correlation ($r = 0.092$, NS). Color scale: red = negative, blue = positive, white = null. Panel C (Sex-stratified outcomes): mean scores by sex among cases (see Table S1 for tests and exact p values).

Appendix C

STROBE Checklist – Case–Control Study (Completed)			
Section/Item	Nº	STROBE recommendation	Where in the manuscript
Title/Abstract	1	(a) Indicate the study design with a commonly used term in the title or abstract; (b) Provide an informative, balanced summary of methods and findings.	Title (“...Case–Control Study”); Abstract (structured IMRaD).
Introduction	2	Background/rationale: explain scientific context and rationale.	Introduction, paragraphs 1–4.
	3	Objectives: state specific aims/prespecified hypotheses.	Introduction, final paragraph (study aims).
Methods	4	Study design: present key elements early.	Methods—Study Design and Participants (“single-center, prospective, observational case–control”).
	5	Setting: locations, relevant dates; recruitment and assessment windows.	Methods—Neuroimaging Acquisition (acute MRI; mean 1.3 ± 0.8 days post-event) and Assessments at 90 ± 14 days; recruiting hospital(s).
	6	Participants: eligibility, sources/methods of case ascertainment and control selection; rationale; (b) matching criteria and number of controls per case if applicable.	Methods—Study Design and Participants (18–70 y; TIA/minor stroke NIHSS ≤ 4; DWI-confirmed; age-matched controls; exclusions: prior dementia, pre-morbid mRS > 1, non-Spanish speakers).
	7	Variables: clearly define outcomes, exposures, predictors, potential confounders/effect modifiers; diagnostic criteria.	Methods—Psychopathological, Cognitive, and HRQoL Assessment (HDRS-17, HAM-A, MoCA, EQ-5D-5L; cut-offs); Neuroimaging variables; clinical covariates (age, sex, mRS, social risk).

Results	8	Data sources/measurement: sources and details of assessment methods; comparability between groups.	Methods—Assessments at 90 ± 14 days (trained, blinded evaluators; standardized protocol); Neuroimaging (1.5 T sequences, blinded neuroradiologists); EQ-5D-5L Spanish value set
	9	Bias: describe efforts to address potential sources of bias.	Methods—Blinding/Training; age-matching for controls; multiplicity control (FDR), HC3 robust SEs, beta-regression sensitivity.
	10	Study size: explain how size was arrived at.	Methods—Regression Modeling (≈10:1 participants:predictors); Limitations (post-hoc power 1−β = 0.84).
	11	Quantitative variables: how handled; groupings and rationale.	Methods—Regression Modeling (z-scoring; binary coding 0/1); cut-offs for HDRS-17, HAM-A, MoCA; EQ-5D-5L utilities.
	12	Statistical methods: (a) all methods incl. confounding control; (b) subgroups/interactions; (c) missing data; (d) matching; (e) sensitivity analyses.	Methods—Statistical Analysis (t/Mann-Whitney/χ²/Fisher; Cohen’s <i>d</i> , OR with 95% CI; Pearson/Spearman; hierarchical multiple regression with ΔR² and incremental <i>F</i> ; mediation via PROCESS v3.5, 5,000 BCa; handling of one missing EQ-5D-5L; HC3 & beta-regression sensitivity).
	13	Participants: numbers at each stage; reasons for non-participation; consider flow diagram.	Results—Sample Characteristics (N = 182; 90 cases/92 controls; n = 89 in regression due to one EQ-5D missing). Optional flow diagram in Supplement.
	14	Descriptive data: characteristics of participants; exposures/confounders; missing data.	Table 1 (baseline); Results—Sample Characteristics; Table S1 (group contrasts and ORs); note on missing EQ-5D-5L in regression set.
	15	Outcome data: numbers/summaries per group.	Results—Psychopathological, Cognitive, and HRQoL; Figure 1 & Table S1.
	16	Main results: estimates with precision (e.g., 95% CI); adjusted and unadjusted; report category boundaries when categorizing continuous variables.	Results—Regression (Models 1–3; R²/ΔR²/ <i>p</i> ; coefficients in Table 3, Table S5); category thresholds for HDRS-17/HAM-A/MoCA.
	17	Other analyses: subgroups/interactions; sensitivity analyses.	Sex-stratified analysis (Figure S1 Panel C; Table S1 sex block); sensitivity (Tables S6–S7); mediation (Tables S3A–S3B; Figure 3).
Discussion	18	Key results summarized with respect to objectives.	Discussion—Principal Findings.
	19	Limitations: discuss sources of potential bias/precision; direction/magnitude.	Discussion—Limitations (case-control/single time point; measures; unmeasured confounding incl. medications/fatigue; generalizability).
	20	Interpretation: cautious overall interpretation considering objectives, limitations,	Discussion—Comparison with Prior Work/Mechanisms/Implications.

21 multiplicity, results from similar studies, and other evidence. Generalisability (external validity). Discussion—

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